Familial Idiopathic infantile arterial calcification presenting as a refractory hypertension and hypercalcemia in neonatal period.

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ABSTRACT

Idiopathic infantilearterial calcification (IIA*C*) is a rare disease characterized by extensive arterial wall calcification. A total of 200 cases have been reported to dateand from India only 5 cases, with most cases diagnosed postnatally and less than 13 cases having been suspected antenatally.Case characteristics: Our case report is first from pediatric department. Message: It is important for clinician to suspect this condition prenatally and so that early diagnosis is associated with improvement in survival rates.

Key words: Idiopathic arterial calcification, hypertension,

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INTRODUCTION

Idiopathic infantile arterial calcification (IIAC) is a rare autosomal recessive disorder associated with widespread calcification and degeneration of the elastic lamina of arteries [1]. The literature on the clinical, radiological, pathological and genetic attributes is vast as compared to that on the management of this life threatening disease. Therapeutic options, though not unavailable, are definitely limited and the reported success rates have been variable. We present a newborn with IIAC with refractory hypertension and persistent hypercalcemia, whose both parents were subsequently found to be carrier of ectonucleotidepyrophosphatase/ phosphodiesterase 1 (ENPP1) mutation on one allele.

CASE REPORT

A baby girl 36 weeks gestation, 2.1 kg, was admitted at 24 hours of life to the Neonatal Intensive Care Unit (NICU) for respiratory distress. She had positive triple test with 3rd trimester antenatal scan showing fetal pericardial effusion. She was born to a 34 year second gravida mother, of anonconsanguinous marriage after emergency caesarean section for polyhydramnios and fetal pericardial effusion. There was no history of perinatal asphyxia.

At admission, she was hemodynamically stable, euthermic and euglycemic. She had tachycardia and tachypnea and required supplemental oxygen. Peripheral pulses were not palpable. She was noticed to have severe hypertension in the second week of life, with mean arterial pressures up to 90 mm Hg. Her metabolic parameters were within normal range with hypercalcemia of 11.0 mg/dl. Her TORCHprofile and karyptyping test were reported normal. A chest x-ray showed massive cardiomegaly and pulmonary edema. An 2D Echocardiogram performed on the day of admission revealed minimal pericardial effusion with severe right ventricular dysfunction which gradually progressed to severe biventricular dysfunction on serial echocardiograms with evidence of calcified ascending aorta, arch of aorta & coronary arteries. An ECG was negative for ischemic changes. USG abdomen revealed diffuse calcification of abdominal aorta with renal arterial stenosis.Computed tomography CT abdomen revealed diffuse rim calcification of the entire aorta & its branches. Neurosonogram and CT scan brain were normal. Laboratory parameters revealed leucocytosis, increased band form cells and a grossly elevated C reactive protein. Blood cultures were sterile throughout. Antibiotics were administered for a two weeks. She was managed with diuretics, digoxin and inotropic support (Dobutamine and Milrinone). Hypertension was initially managed with oral amlodipine and later on she was switched over to captopril 1.2 mg/kg/day.

In view of antenatal evidence of early hydrops (pericardial effusion), polyhydramnios, post natal evidence of diffuse calcification of the arterial system, renal artery stenosis and hypertension, a diagnosis of idiopathic infantile arterial calcification was made. She was commenced on calcium chelation therapy with low dose IV Palmidronate (0.1mg/kg) on the eleventh day of life. She improved over a week with stabilization of the heart rate and improved peripheral perfusion. She did not have any adverse effects of diphosphonate therapy. She was monitored with regular renal function tests and serum calcium. The plan was to switch over to oral etidronate therapy on follow up. Repeat ultrasound scans showed resolution of renal arterial calcification. Repeat echocardiograms showed normalization of the ventricular function.

He was also evaluated for other causes of Hypercalcemia. His Parathyroid and Vit D levels were within normal range. Molecular genetic testing for Myoclonic epilepsy with ragged red fibers (MERRF), Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) and Neuropathy, Ataxia, and Retinitis Pigmentosa (NARP) syndrome were negative. We could not do mutation analysis on the patient as she died at six month of age. Both the parents were positive of ENPP1 mutation on one allele.

Fig:1. Computed tomography abdomen revealed diffuse rim calcification of the entire aorta & its branches

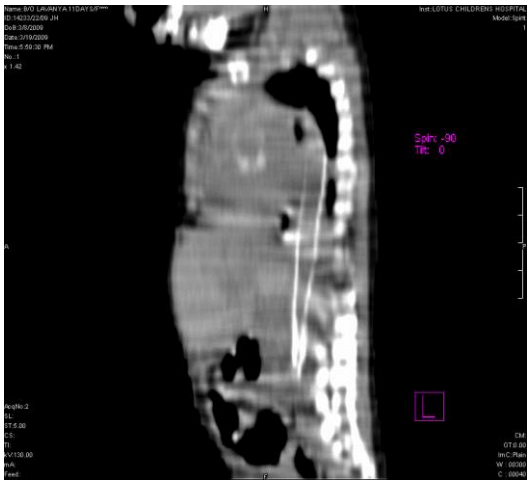
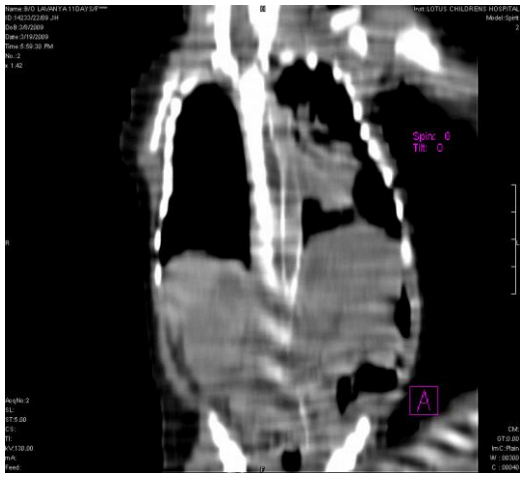


Fig:2. Computed tomography abdomen revealed diffuse rim calcification of the entire aorta & its branches



DISCUSSION

Idiopathic infantile arterial calcification (IIAC) was described by Bryant and White in 1901[2]. So far approximately 200 reports of this disease have been published worldwide Most of the affected infants die before the age of 6 months, and very few have survived for more than 1 year[3]. IIAC is a rare autosomal recessive disease characterized by extensive calcification of medium and large arteries including the aorta, coronary arteries, and renal arteries. Loss-of-function mutation in ectonucleotidepyrophosphatase/phosphodiesterase 1(ENPP1) gene was found in 80% of cases[4]. This mutation is found to cause a loss of function by decreased levels of inorganic pyrophosphate which normally inhibits extracellular matrix calcification. Although most cases of IIAC are diagnosed at autopsy, there have been reports of diagnosis prior to death based on characteristic findings seen on imaging studies. These include arterial calcification, thickened myocardium, and aortic ring appearance caused by aortic wall calcification [5].

The clinical manifestations of the disease are secondary to calcification of the large and medium sized arteries including the aorta, coronary and renal arteries [6]. It can present in the antenatal period asnon immune hydrops fetalis or polyhydramnios. Post natally, the majority of the neonates can present in the first month of life with features of cardiac dysfunction with respiratory distress, poor feeding, poor peripheral perfusion and failure to thrive. They can also present with severe, refractory hypertension secondary to decreased vascular compliance and renal artery stenosis and its antecedent complications. *Farquhar et al have reported a neonate with idiopathic infantile arterial calcification with persistent pulmonary hypertension* [7]. Mortality rates of upto 85 % have been described in the first 6 months of life [8]. Mortality is usually secondary to cardiac dysfunction and occlusion of the coronary arteries.

Various treatment modalities such as thyroid extract, estrogens, steroids and diphosphonates have been tried with different success rates [9]. Kim A Ramjan et al have described successful resolution of the arterial calcification with low dose third generation diphosphonates therapy in a neonate[10].Inge M. van der Sluis have reported successful use of etidronate therapy and long term follow up upto twenty five years of age[11]. Graham Stuart et al described failure of diphosphonate therapy in their patients [12].The exact dose of bisphosphonates for disease treatment is not known, and data reported in theliterature vary from 5 mg/kg per day of disodium etidronateover a period of a few weeks to 15–35 mg/kg per dayover 18 months[13].Glatz et al have discussed a potential role for cardiac transplantation in view of lack of definitive pharmacological therapy[8]. Prolonged etidronate use in patients with IIAC has been associated with severe skeletal toxicity, including radiographic findings resembling hypophosphatasia (pan craniosynostosis, bowing of long bones, metaphyseal cupping and fraying, radiolucent tongues) or osteopetrosis (osteosclerosis and femoral Erlenmeyer flask deformity). Given the risk of severe adverse skeletal effects with prolonged bisphosphonate treatment and the failure of calcifications to reappear after discontinuation of treatment, some authors recommend close monitoring for resolution of arterial calcifications during treatment so that use of bisphosphonates can be discontinued as soon as possible [14]. In our case we did not find any side effects of the therapy. The effect of administration of bisphosphonates may vary according to the severity of the disease.

Studies demonstrated that homozygous or compound heterozygous loss-of-function mutations in *ENPP1* result in IIAC in about 80% of the cases [15]. Accordingly, in the family presented here, *ENPP1*mutational analysis was performed in the parents of an index case with clinically proven IIAC. Although the clinical diagnosis of IIAC is based on clinical features and typical radiographic signs, molecular analysis of *ENPP1* is mandatory for genetic counseling in the affected family

CONCLUSION

There is an urgent need to use molecular tests to confirm the diagnosis and understand the risk-benefit ratio and also the potential risks involved. Genetic counseling for IIAC is very important as the disease is transmitted in an autosomal recessive manner. Hence, it is recommended that along with investigations like Computed Tomography, more advanced investigations such as fetal echocardiogram and molecular analysis of ENPP1 should be

included in the work up of IIAC. It will help the clinician to treat as well as help in counseling of the affected parents for further pregnancies.

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